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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/063,586
Filing Date: May 03, 2002
Appellant(s): EATON ET AL.

Anne Marie Kaiser
For Appellants

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 16, 2005, appealing from the Office action mailed June 14, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner as provided by the Appellants which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

A Notice of Appeal has been tiled in the related Application Nos. 10/063,519; 10/063,560; 10/063,617; 10/063,661 and 10/063,713. A Notice of Appeal and an Appeal Brief have also been filed in the related Application Nos. 10/063,530; 10/063,540; 10/063,578; 10/063,584; 10/063,616; 10/063,648; 10/063,652; 10/063,653; 10/063,659; 10/063,534; 10/063,591; 10/063,587; 10/063,592 and 10/063,660.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner: the rejection of claims 4, 5 and 12-17 under 35 USC 112, first paragraph, written description, in view of Appellants' arguments.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Haynes et al., Proteome analysis: Biological assay or data archive, Electrophoresis, 19:1862-1871, 1998.

Hu et al., Analysis of genomic and proteomic data using advanced literature mining, J. Proteome Res., 2:405-412, June 2003.

Fessler et al., A genomic and proteomic analysis of the activation of the human neutrophil by lipopolysaccharide and its mediation by p38 mitogen-activated protein kinase, J. Biol. Chem. 277(35):31291-31302, 30 Aug. 2002.

Chen et al., Discordant Protein and mRNA Expression in Lung Adenocarcinomas. Molecular & Cellular Proteomics, 1.4. 304-313, 2002

Konopka et al., Variable expression of the translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients, Proc. Natl. Acad. Sci. USA, 83:4049-4052, June 1986.

Alberts et al. Molecular Biology of the Cell, 4rd Edition 2002 (New York:Garland Publishing), pp. 302, 363-364, 379, 435.

Alberts et al. Molecular Biology of the Cell, 3rd Edition 1994 (New York:Garland Publishing), pp. 403-404, 453.

B. Lewin, Genes VI, 1997.

Zhigang et al., World Journal of Surgical Oncology 2: 13, 2004.

Meric et al., Translation initiation in cancer: A novel target for therapy, Molecular Cancer Therapeutics, 1:971-979, 2002.

Gygi et al., Correlation between protein and mRNA abundance in yeast, Mol. Cell. Biol., 19(3):1720-1730 Mar. 1999.

WO 01/16318 A2 Eaton et al. 03-2001

WO 00/12708 A2 Baker et al. 03-2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

Claims 6-8 and 11-17 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to a polypeptide. The specification asserts a number of utilities for both the polypeptide and encoding polynucleotide, however, these utilities are not specific and substantial or well established. For example, in Example 11 (page 133), it is asserted that the polypeptide may be used as an antigen to make antibodies. Because neither the physiological nor the clinical significance of the polypeptide is known, and because the prior art does not support a very close structural relationship to a well described family of known proteins by both structure and function, the polypeptide does not have utility as required by 35 USC 101. If the polypeptide antigen does not have utility, then the antibody which binds it (or method of making the antibody) does not have a specific and substantial utility.

Another example of utility is in drug screening and rational drug design (Examples 12 and 13, respectively). The methods involve screening for "agents which can affect a PRO polypeptide-associated disease or disorder" (p. 135, ¶[0507]). No disease or disorder is known to be associated with the claimed polypeptide or encoding polynucleotide. In order to discern a

utility for the claimed polypeptide through drug screening in the absence of guidance about which type of disease or disorder the polypeptide causes or how its involvement could lead to treatment, screening for drugs by using the polypeptide would still require further and undue experimentation to determine the significance of an agent that somehow influenced the polypeptide's function.

Another possible utility comes for the finding that the encoding polynucleotide is "more highly expressed" in normal stomach and lung as compared to stomach and lung tumor tissue (Example 18, p. 142). There is no guidance on how to use this information. No levels (relative or absolute) are disclosed. This information is too sparse to support a substantial use for the encoded polypeptide to be used as a diagnostic marker for stomach or lung tumor. Even if the polynucleotide has utility as a tumor marker, the encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in stomach or lung tumor *versus* normal tissue. It is not known what the protein does or if the level of the protein of SEQ ID NO:78 in stomach or lung tumors corresponds to nucleic acid transcript level, *i.e.*, if decreased mRNA expression in tumors corresponds to a decrease in amount of expressed protein.

There is influential prior art to support the unpredictibility concerning the correspondence of mRNA to protein levels. For example, Haynes et al. (Electrophoresis 19 : 1862-1 87 1 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1 863, second paragraph, and Figure 1). Haynes et al. provides evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Additionally, Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002, cited by Appellants in the IDS filed 9/15/05 as reference #3) who examined lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on p. 31300) stated, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into

mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." Fessler et al. warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." Chen et al. (Mol. Cell Proteomics 1.4:304, 2002, cited by Appellants in the IDS filed 7/5/05 as reference #17) studied 165 proteins from lung adenocarcinoa tumors expressed by 98 individual genes Their findings provide further evidence that one cannot assume the level of mRNA will correlate with the level of expressed protein for any given gene or any given protein (paragraph bridging pages 312-313):

> The results of this study indicate that the level of protein abundance in lung adenocarcinomas is associated with the corresponding levels of mRNA in 17% (28 proteins) of the total 165 protein spots examined. This was substantially higher than the amount predicated to result from chance alone (which was 5.1) and suggest that a transcriptional mechanism likely underlies the abundance of these proteins in lung adenocarcinomas. We also demonstrated that the expression of individual isoforms of the same protein may or may not correlate with the mRNA, indicated that the separate and likely post-translational mechanisms account for the regulation of isoform abundance. These mechanisms may also account for the differences in the correlation coefficients observed between stage I and stage III tumors, indicating that specific protein isoforms show regulatory changes during tumor progression.

Further it was shown (p. 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with their encoded proteins. Given the unknown amount that mRNA copy number of PRO1357 increased in tumors, and the evidence provided by Haynes et al., Hu et al. (cited in the previous Office action), Fessler et al. and Chen et al., one skilled in the art would not have assumed that a small increase in mRNA copy number would correlate with significantly increased polypeptide levels. Given how small the unknown amount that DNA copy number of PRO1357 decreased in tumors, and the evidence provided by Haynes et al., Hu et al.

Fessler et al. and Chen et al., one skilled in the art would not have assumed that a small decrease in gene copy number would correlate with significantly increased mRNA or polypeptide levels. The level of decrease of the encoding nucleic acid is not disclosed. One skilled in the art would have to do significant further research to determine whether or not the PRO1357 polypeptide levels decreased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, *i.e.*, it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Note that the invention must have a specific and substantial utility.

Lastly, in Figure 78, it is indicated that the polypeptide shows some structural similarity to LBP, BPI and CETP family proteins; however, the type of relationship is not disclosed. No important features common to all the proteins are disclosed. The level or pattern of the similarity is not discussed. The skilled artisan could not use this information to establish a specific and substantial use the claimed polypeptide.

For these reasons, there is no substantial and specific utility for the claimed polypeptide.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 6-8 and 11-17 remain also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed polypeptide because no definite function or directly associated disease has been determined for the protein of SEQ ID NO:78, and there is no definite function supported by the prior art. No function can be reasonably assigned based on its homology to another protein(s).

Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is a polypeptide encoded by a nucleic acid with no known specific association other than that asserted by Appellants of underexpression in stomach and lung tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in stomach and lung tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical property. Proteins not identical to SEQ ID NO:78 have not been shown to exist in nature, let alone in stomach or lung tissue. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though none as a tumor marker were identical or highly similar to SEQ ID NO:77. Therefore, the connection of SEQ ID NO:77 to tumors was not known. The prior art is silent with respect to activity of PRO1357 or its relationship to a family of proteins with conserved structure and function. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. The breadth of the claims is broad, encompassing structural variation. There is very little guidance or direction about using the claimed polypeptide except that the encoded nucleic acid of SEQ ID NO:77 is underexpressed in stomach and lung tumors. The specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA

libraries from each tumor tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

Claim Rejections - 35 USC § 102

Claims 6-8 and 11-17 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/161318 or WO 00/12708.

WO 01/161318 teaches the polypeptide of SEQ ID NO:78 (see Fig. 78), as well as a polypeptide comprising the extracellular domain with or without its signal sequence (claim 20). A chimeric polypeptide wherein SEQ ID NO:78 is fused to an Fc region of an immunoglobulin is also taught (p. 52, lines 30-37).

WO 00/12708 teaches the polypeptide of SEQ ID NO:128 (see Fig. 72), as well as a polypeptide comprising the extracellular domain with or without its signal sequence (p. 295, lines 14-27). A chimeric polypeptide wherein SEQ ID NO:128 is fused to an Fc region of an immunoglobulin is also taught (p. 293, lines 1-4).

(10) Response to Argument

Appellants argue (pages 7) that the phrase "immediate benefit to the public" does not necessarily have to mean the invention is "currently available" to the public in order to satisfy utility requirements. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining 'substantial' utility." (MPEP § 2170.01). The argument has been fully considered, but is not persuasive. That section of the MPEP also states that when "further research is required to reasonably confirm the asserted utility, the claims do not meet the requirements of 35 USC 101." The specification has failings which the Examiner pointed out. While current availability of a claimed invention is not always necessary, the invention must still meet the requirements of 35 USC 101 and 112, first paragraph. For the reasons discussed here and in the previous Office action, it is maintained the specification does not support utility or contain an enabling disclosure, and the evidence submitted, including declarations, does not overcome the insufficiencies of the disclosure. While other asserted utilities were discussed in

previous Office actions such as drug screening and microarray analysis, these utilities are not substantial for the reasons previously stated.

Appellants argue (top of p. 8 through p. 9, middle of p. 11) that statements of utility are presumed to be true unless they are incredible. The argument has been fully considered, but is not persuasive. Credibility has not been raised as an issue.

Appellants argue (bottom of p. 10) that because the PRO1357 mRNA was held to have utility, the claimed polypeptide has a specific utility as a cancer diagnostic too, particularly for stomach and lung. The argument has been fully considered, but is not persuasive. While it is agreed that the polynucleotide of SEQ ID NO:77 has this specific utility, it is not agreed that the polypeptide of SEQ ID NO:78 does. The reasons for this have been discussed above, including relative or absolute levels of the difference(s) in PRO1357 protein level in tumor *vs.* normal stomach or lung tissue, the lack of information about particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), the lack of information about repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, unknown necessary sample size or expression level range for normal and tumor tissues and the unpredictability of correlation mRNA and protein expression levels, it is maintained that the claimed invention is not supported by a substantial or specific utility nor is it enabled.

Appellants argue (top of p. 11) that the specification discloses that PRO polypeptides may by used to generate anti-PRO antibodies which are useful as diagnostic tools. The argument has been fully considered, but is not persuasive. If the claimed protein to which an antibody binds is not enabled for how to use and lacks utility, then the antibody likewise has no use. The sole ability to bind a protein is not sufficient to support enablement or a substantial utility.

Appellants argue (pages 11-13, 23-26, 38) that the Konopka et al. reference deals with gene amplification instead of cDNA or mRNA levels compared to protein levels and thus is not relevant to the instant application, since the information in Example 18 of the instant application deals with mRNA expression instead of gene amplification. The Examiner agrees that gene amplification was not presented in Example 18 and also that Konopka does not address the issue at hand of correspondence of levels between mRNA and protein. However, Haynes et al. (previously cited and discussed) does and supports the inability to reasonably expect the level of mRNA to correspond to the level of its encoded protein. Further, other references cited by

Appellants also support the lack of reasonable expectation. Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002, cited by Appellants in the IDS filed 9/15/05 as reference #3) examining lipopolysaccharide-activated neutrophils (col. 2, beginning of last paragraph on p. 31300) states, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." Fessler et al. warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels." Chen et al. (Mol. Cell Proteomics 1.4:304, 2002, cited by Appellants in the IDS filed 7/5/05 as reference #17) studied 165 proteins from lung adenocarcinoa tumors expressed by 98 individual genes Their findings provide further evidence that one cannot assume the level of mRNA will correlate with the level of expressed protein for any given gene or any given protein (paragraph bridging pages 312-313):

> The results of this study indicate that the level of protein abundance in lung adenocarcinomas is associated with the corresponding levels of mRNA in 17% (28 proteins) of the total 165 protein spots examined. This was substantially higher than the amount predicated to result from chance alone (which was 5.1) and suggest that a transcriptional mechanism likely underlies the abundance of these proteins in lung adenocarcinomas. We also demonstrated that the expression of individual isoforms of the same protein may or may not correlate with the mRNA, indicated that the separate and likely post-translational mechanisms account for the regulation of isoform abundance. These mechanisms may also account for the differences in the correlation coefficients observed between stage I and stage III tumors, indicating that specific protein isoforms show regulatory changes during tumor progression.

Further it was shown (p. 309, col. 2, 5th line) that, "In addition to differences in the relationship between mRNA levels and protein expression among separate isoforms, some genes with very comparable mRNA levels showed a 24-fold difference in their protein expression. Genes with comparable protein expression levels also showed up to a 28-fold variation in their mRNA levels." Chen showed that not only with mRNAs that encode a single protein but also with nucleic acids that encode multiple isoforms, only a minority of mRNAs showed a correlation in levels of expression with their encoded proteins. Given the unknown amount that mRNA copy

number of PRO1357 increased in tumors, and the evidence provided by Haynes et al., Hu et al. (cited in the previous Office action), Fessler et al. and Chen et al., one skilled in the art would not have assumed that a small increase in mRNA copy number would correlate with significantly increased polypeptide levels. The level of increase of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO1357 polypeptide levels increased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, *i.e.*, it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellants' claimed invention is incomplete. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form that can be used without necessary further experimentation.

Appellants argue in the first full paragraph of p. 13 that there is a discrepancy between the status of utility for the PRO1357 nucleic acid as discussed in the instant application between the Office action of March 8, 2005 and June 14, 2005. The argument has been fully considered, but is not persuasive. There is in fact no discrepancy because on June 14, 2005, the previously maintained rejection of the nucleic acid under 35 USC 101 was withdrawn, though lack of enablement was maintained. It is appropriate for Appellants to address the arguments in the most recent Office action as that has the most up to date status of the claims.

Appellants argue on pages 14-15 and 34 and 45 that *In re Brana* states that the USPTO has the initial burden of showing "that one of ordinary skill in the art would reasonably doubt the asserted utility." The argument has been fully considered, but is not persuasive. While *Brana* did deal with a rejection under 35 USC 112, first paragraph, the rejection was directed toward utility--specific, substantial and credible use. While it is true that administration of a pharmaceutical to a human is not always necessary for either utility or enablement nor that a protein have been used diagnostically, one must know how to use the invention without undue experimentation. In the instant situation, Appellants claim a polypeptide which the USPTO has presented evidence (*e.g.*, Haynes et al., Hu et al., Fessler et al. and Chen et al.) showing that for eukaryotic polypeptides in general one cannot assume that it is more likely than not that the polypeptide will have a level of expression comparable to that of its encoding mRNA in one tissue type compared to a matched tumor tissue type even if the encoding nucleic acid in the

normal and tumor tissues does have detectably different expression levels. Additionally, claims 14-17 are drawn to a polypeptide which is at least 95% or 99% identical to SEQ ID NO:78, which can be used to generate antibodies which can specifically detect the polypeptide of SEQ ID NO:78 in lung or stomach tissue samples, of which it is maintained the disclosure does not enable the use. The USPTO has met the burden of showing one skilled in the art would reasonably doubt the asserted utility by showing that the correspondence between mRNA and protein levels is not predictable as previously discussed.

Appellants argue (pages 15 through top of p. 17) that the PTO maintains that the specification fails to provide particular information and the PTO has applied an improperly high standard by requiring additional data and evidence be disclosed in order for Appellants to initially establish a utility for the claimed polypeptides, such as type of stomach and lung tumor used and probability of detection, beyond the evidence already provided (in Example 18 and presented in the Declarations and other exhibits). The argument has been fully considered, but is not persuasive. There are a number of significant unknowns in the specification that the declarations, exhibits and arguments do not fill in. One example is that there are several types of cancers for any type of tissue, for example, squamus cell or adenocarcinoma, and the type which was identified in the instant application is not disclosed. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated previously, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels in normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a currently available form. Other gaps in information include, for example, tumor type (etiology), repeatability of the differential

expression both in terms of frequency/prevalence and quantity/sensitivity, and a basis for reasonably expecting that a change in mRNA level causes a corresponding change in protein level. It is maintained that significant further research would be necessary to use the claimed invention.

Appellants argue on pages 16 and 26-27 that the PTO has not met the initial burden of refuting that is more likely than not the claimed polypeptide does not have the asserted utility and that there is no evidence of record to establish that one of ordinary skill in the art would reasonably doubt that the disclosed polypeptide is differentially expressed in certain tumors and can be used as a diagnostic tool. The argument has been fully considered, but is not persuasive. One should not confuse credibility with specific and substantial use or enablement. The Examiner maintains that as a whole, the prior art does not provide a reasonable expectation that the level of expression of the nucleic acid of SEQ ID NO:77 positively correlates with the level of expression of the protein of SEQ ID NO:78. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. Protein levels do not need to be "accurately" predicated, but relative or absolute levels or information about repeatability are critical for the skilled artisan to be able to use the instant invention without having to do further significant research. While absolute values are not necessary, certain criteria must be met for relative levels to be meaning for in terms of utility. Some criteria are what the relative difference is (*e.g.*, 0.5 times more or 10 times more expression), repeatability (*e.g.*, how may different stomach or lung tumor samples were used), whether the claimed polypeptide is underexpressed in the tissues in which that the PRO1357 polynucleotide is underexpressed.

Appellants argue (p. 17) that the results of Hu et al. (J. Proteome Res., 2003, previously cited) are not surprising and provide little if any information about genes with less than 5-fold differential expression tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are

biologically meaningful." As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are significant.

Appellants argue (pages 18-19, end of p. 20, top of p. 25) that the results of Hu et al. do not show a lack of correlation between microarray data and biological significance, have statistical flaws and are applicable only to estrongen-postive breast tumors. The argument has been fully considered, but is not persuasive. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. As discussed above, it is not clear that the expression changes listed in Example 18 of the instant specification are statistically significant. While Hu et al. examined just one kind of cancer, the results taken together with others discussed by the Examiner, support the inability of the skilled artisan to make assumptions about the correlation of nucleic acid expression data with expressed protein data. While neither a gene or the encoded protein need not have a biologically meaning role in disease, one skilled in the art must be able to use it and it must be supported by a substantial utility.

Appellants argue (pages 19-20) that the role of a gene in a cancer is not necessary to enable its use as a diagnostic tool for tumor detection. The argument has been fully considered, but is not persuasive. It is correct that the role of a gene need not be known, but the specification and/or prior art needs to enable that particular gene to be used diagnostically. In this case, the prior art provides no information about the use of the gene and the specification does not provide an enabling disclosure for use of the PRO1357 nucleic acid or protein as a diagnostic tool for stomach or lung tumors based on differential expression for the reasons discussed above and in previous Office actions. As to the claims drawn to proteins not identical to SEQ ID NO:78, even if SEQ ID NO:78 was enabled for a diagnostic tool, proteins not identical would not be because they would not be expected to be present in tumors and what parts of the protein are antigenic and necessary for proper antibody binding (and production) for the protein to be useful as an antigen to make antibodies that would recognize the protein of SEQ ID NO:78 are not disclosed.

Appellants argue (p. 19) that like "the mere identification of a pharmacological activity", identification of an altered expression provides 'immediate benefit to the pubic'. See MPEP § 2107.01. The argument has been fully considered, but is not persuasive. This citation relates to the Court's decision in *Nelson v. Bowler.* In that decision, the CCPA says that specific

therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. In this instance, pharmacological activity is not the same as altered gene expression. In *Nelson,* the court held that the compound of which utility was in question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility. There are no test results to correlate the presence of PRO1357 polypeptide with a diagnostic for stomach or lung tumor. Also in the same section of the MPEP, In *In re Jolles* (CCPA 1980), finding of utility was based on the close structural relationship to a prior art compound known to possess therapeutic utility. PRO1357 has no known relationship. It is maintained that the instant application has not established the use of a polypeptide of SEQ ID NO:78 and utility as a cancer diagnostic. The findings of underexpression of the nucleic acid of SEQ ID NO:77 cannot be assumed to correlate to the underexpression of the encoded polypeptide in the same tissues.

Appellants argue (pages 21-23, middle of 25, 38) that the report of Haynes et al. and Gygi et al. (previously cited) do not support the Examiner's position that mRNA levels do not correlate with protein levels, pointing out that Haynes did not look at *single* genes and corresponding protein level. Appellants' point to the correlation coefficient of 0.935 in Haynes et al., saying that this shows a correlation instead of the lack of one. The argument has been fully considered, but is not persuasive. A complete reading of Haynes and Gygi et al. continues to support the reliance on Haynes et al. However, a full reading of Haynes et al. clarifies the data (p. 1726, first full paragraph):

> For the entire group (106 genes) for which a complete data set was generated, there was a general trend of increased protein levels resulting from increased mRNA levels. The Pearson product moment correlation coefficient for the whole data se (106 genes) was 0.935. This number is highly biased by a small number of genes with very large protein and message levels. A more representative subset of the data is shown in the inset of Fig. 5. It shows genes for which the message level was below 10 copies/cell and includes 69% (73 of 106 genes) of the data used in the study. The Pearson product moment correlation coefficient for this data set was 0.356.

Contrary to Appellants' assertion that Figures 5 and 6 of Gygi support the correlation of mRNA and protein levels, Gygi et al. show in Figure 5 the same figure as Fig. 1 of Haynes and show in Fig. 6, what is described for the Pearson correlation coefficients in the cited paragraph above. Gygi et al. say beginning in the last sentence in col. 1 of p. 1727 that, "The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells." As to correlation of an individual gene, Gygi et al. and Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described above by Haynes et al. Each point in the figures of Haynes et al.and Gygi et al. are individual genes (see Fig. 1 and Figs. 5-6, respectively). Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1357 nucleic acid was isolated).

Appellants also argue (pages 22-23) that Haynes et al. is not relevant to the instant application since yeast cells were used and did not compare mRNA and protein levels from the same yeast cells. Additionally, Haynes et al. discuss only steady-state levels, which is a different issue than the changing levels discussed by Appellants. The argument has been fully considered, but is not persuasive. Haynes et al. point to a great unpredictability about expression of a nucleic acid and its encoded protein. Predicting a correlation for any single gene is more difficult than for a large pool of genes showing a general trend. This can be seen by the low 0.356 correlation coefficient described by Haynes et al. Each point in the figures of Haynes et al. is an individual gene (see Fig. 1). Therefore, the authors did examine single genes. Haynes et al. supports the rejections of record and also says that the results, which are from eukaryotic cells, are expected to be representative for mammalian cells (*e.g.*, like the human cell from which the PRO1357 nucleic acid was isolated). The instant specification did not show that changing levels

of PRO1357 mRNA lead to respective changing levels in PRO1357 protein. It showed that there is some unknown amount of SEQ ID NO:77 produced at a lower level in normal stomach and lung and than stomach and lung tumor tissue. The unknowns continue in terms of samples used, repeatability, sensitivity, unknown relative or absolute amounts of mRNA in the tissues, etiology of tumor tissue used, and whether the difference extends to the a difference in encoded protein levels.

Appellants argue (pages 26-27 and 46) that it is "more likely than not" that the expression of the polypeptide will correlate with encoding nucleic acid expression in tumors (*i.e.*, at decreased levels) and that the law does not require absolute levels of expression. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential art of record that requires the Examiner maintain that as a whole, the art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:77 positively correlates with the expression of the protein of SEQ ID NO:78. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. Neither protein nor nucleic acid levels need to be "accurately" predicated, but relative or absolute levels or information about repeatability are critical for the skilled artisan to be able to use the instant invention without having to do further significant research. While absolute values are not necessary, certain criteria must be met for relative levels to be meaning for in terms of utility. Some criteria are what the relative difference is and repeatability (*e.g.*, how may different tumor samples were used).

Appellants argue (page 28 and 35) that in paragraphs 6 and 7 the first declaration by Dr. Grimaldi (submitted 9/24/04) explains that the semi-quantitative analysis used for Example 18 of the instant application is sufficient to determine if a gene is over- or under-expressed in a tumor compared to normal cell, with detectability of at least 2-fold differences, and the relative not the absolute difference is what matters. This argument has been fully considered but is not deemed persuasive. The conclusory statements in the declaration do not support a substantial utility or enable the invention because they do not fill important gaps in the disclosure needed to allow the skilled artisan to use the invention without significant further experimentation, such as

expression level range for normal and tumor tissues, specific types of lung or stomach tumors detectable, and probability of detection for any particular lung or stomach tumor type (*e.g.*, whether one would reasonably expect underexpression in 10/10 or 1/20 tumors tested). Even though the detection in Example 18 of the specification was carried out using cDNA libraries from tumor and normal tissue sample and, according to the declaration, the libraries were made from pooled samples of tissues. This information does not fill the above discussed gaps. It is noted that Grimaldi in paragraph 6 of the declaration describes the detection as "semi-quantitative" and the specification for Example 18 as "standard quantitative". The declaration also says (¶5) that "Data from a pooled sample are more likely to be accurate than data from a single individual." This begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. Clinical diagnostics are not usually geared toward a populous but toward an individual's particular condition. While a "relative difference in expression between normal tissue and suspected cancerous tissue" can be informative, without more specifics about necessary sample size, expression level range for normal and tumor tissues, types of esophageal tissue that can used, and other questions, the specification has not provided the invention in an enabling or substantial form. Even if tissue samples are pooled, about which the first Grimaldi Declaration says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance. If a clinician took a stomach tissue sample from a patient with suspected stomach cancer, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO:77 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? While the 6th paragraph of the first Grimaldi Declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a specific and substantial use of the nucleic acid in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size,

expression level range for normal and tumor tissues, types of stomach or lung tissue that can used, and other questions, the specification has not provided the invention in a form readily usable by the skilled such that *significant* further experimentation was unnecessary. Therefore, even accepting Dr. Grimaldi's opinion, the declaration is insufficient to overcome the rejection of the claims under 35 USC 101 and 112, first paragraph, for the reasons discussed above.

Appellants argue (paragraph bridging pages 28-29, 35, 37) that "Office personnel must accept option from a qualified expert that is based upon relevant facts whose accuracy is not being questions." First, it is important to note that the instant specification provides no specific information regarding decreased mRNA levels of PRO1357 in tumor samples relative to normal samples. Only gene expression data represented as "underexpressed" was presented. Second, the declaration does not provide data such that the Examiner can independently draw conclusions. Only Dr. Grimaldi's conclusions are provided in the declaration. While several articles are provided as evidentiary support to Dr. Grimladi's statement that it remains a dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide (¶5), two of the references are below and do not address the lack of substantial utility or enablement of PRO1357 polypeptide. While one can find references that support Dr. Grimaldi's statements, other previously cited literature illustrates the unpredictability inherent in correspondence between mRNA and protein levels.

In the second Declaration of Dr. Grimaldi filed 9/24/04, Appellants argue (paragraph bridging pages 29-30, 37, 44) that increased or decreased gene expression correlates with increased or decreased polypeptide expression, respectively, in a vast majority of the cases, with no response from the Examiner about this. This argument has been fully considered but is not deemed persuasive. While ¶4 of the declaration describes mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1357 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the

development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t(5;14), no translocation of PRO1357 is known to occur. Paragraph 6 of the declaration says that even when amplification of a cancer marker gene does not result in significant over- or under-expression of the corresponding gene product, that in itself provides important information for cancer diagnosis and treatment. However, there is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. It remains that, as evidence by Haynes et al., Fessler et al. and Chen et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This is further borne out in paragraph 6, which proposes further experimentation, should Appellants' assertions be erroneous. As can be seen from previous Office actions (*e.g.*, 12/13/04), the concepts set forth in the second Dr. Grimaldi declaration had been addressed and not found persuasive as additionally discussed in this Answer.

Appellants argue (pages 30, 36-37) that the declaration by Dr. Polakis also filed 9/24/04 supports both utility and enablement of the instant invention. In the declaration Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. The declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular

biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

Appellants cite Alberts et al. (Molecular Biology of the Cell, 1994 and 2002) for showing the steps at which eukaryotic gene expression can be controlled, correlating transcription with protein production (paragraph bridging pages 30-31 of Brief). This argument has been fully considered but is not deemed persuasive. The teachings of Alberts are contrary to the teachings of Konopka et al. who showed an example of a gene that does not regulate protein expression levels as discussed by Appellants (page 21 of the Brief). It is noted that the field of proteomics was very new in 1994, when the first cited teachings of Alberts were published. Additionally, the references of Haynes et al., Chen et al. and Fessler et al. clearly show that one cannot reasonably expect that for any given mRNA the level of protein produced therefrom will correlate with the amount of mRNA.

Appellants also cite Lewin (Genes VI, 1997) and Zhigang et al. (World J. Surg. Oncol, 2004) to support the ideas of Alberts et al. (above), with the example of Zhigang et al. showing that there is a high correlation between PSCA protein and mRNA expression (pages 31-32 of Brief and p. 34, last paragraph, dealing with lack of explanation of why gaps in the specification need to be filled). This argument has been fully considered but is not deemed persuasive. Lewin teaches the same idea that Alberts et al. do. There is convincing evidence of record that in some cases transcription is the controlling factor but in other it is translation. The Zhighan find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application we have no correlation. There is no suggestion of multiple tumors tested. There are [0530] just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect underexpression in 10/10 or 1/20 tumors tested for the PRO1357 nucleic acid and/or protein. If Zhinghan et al. had obtained only a 5%

correlation, it is doubtful he would have concluded that the nucleic acid would be a promising molecular marker.

Appellants argue (p. 32) that Meric et al. (Mol. Cancer Ther., 2002) says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this statement is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use as discussed above and the art that teaches unpredictability concerning a correlation between protein and mRNA expression levels. Further reading of Meric et al. seems to teach away from Appellants' claim that there is a correlation between decreased mRNA level and protein level. For example, Meric et al. discloses that variation in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974).

Appellants argue (p. 33) that the asserted utility is specific. It is specific to a type of lung or stomach tumor though it is maintained that is not substantial or enabled for the reasons discussed in previous Office actions and here.

Appellants argue (pages 38-39) that the Examiner has dismissed textbook references, articles and declaration in maintaining the rejections. The argument has been fully considered, but is not persuasive. There are a number of significant unknowns in the specification that the declarations, exhibits and arguments do not solve. One example is that there are several types of cancers for any type of tissue, for example, squamus cell or adenocarcinoma, and the type which was identified in the instant application is not disclosed. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966) 696, in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated previously, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without

more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form. Other gaps in information include, for example, tumor type (etiology), repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity, and a basis for reasonably expecting that a change in mRNA level causes a corresponding change in protein level. It is maintained that the instant invention does not have a substantial utility and specific benefit does not yet exist in a currently available form.

Appellants argue (pages 39 and paragraph bridging 44-45) that in *Brenner v. Manson*, 383 US 519, 148 USPQ 689 (1966) at 691, the Court held that "where a claimed process produces a known product it is not necessary to show utility for the product." Appellants say the Examiner points to no facts whatsoever in the decision to support the position that finding in *Brenner* are analogous to the instant application. The argument has been fully considered, but is not persuasive. Appellants' quote is taken from the reasoning of the court to allow an interference to proceed. The quoted idea of utility was what the Supreme Court set out to clarify and rectify with standing Court decisions. At 696, the Supreme Court stated that they "find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product." The Supreme Court also discussed (694):

> Even on the assumption that the process would be patentable were respondent to show that the steroid produced had a tumor-inhibiting effect in mice, [17]we would not overrule the Patent Office finding that respondent has not made such a showing. The Patent Office held that, despite the reference to the adjacent homologue, respondent's papers did not disclose a sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics. Indeed, respondent himself recognized that the presumption that adjacent homologues have the same utility [18]has been challenged in the steroid field because of "a greater known unpredictability of compounds in that field." [19] In these circumstances and in this technical area, we would not overturn the finding of the Primary Examiner, affirmed by the Board of Appeals and not challenged by the CCPA.

The above situation is analogous to that of the instant application because its claimed invention, the PRO1357 protein and related proteins have not been shown to have a sufficient likelihood of

being used as a cancer diagnostic for the reasons previously discussed. Also, in the proteomic art there is a "known unpredictability" concerning the correlation of mRNA and protein levels.

Appellants discuss *In re Kirk (CCPA 1967)* on pages 39 and 45, in which the assertion that a man-made steroid with biological activity was insufficient without information in the specification as to how the biological activity could be practically used. This case does not refute the current rejections.

Appellants argue (pages 40-41, 43 and 45) that in *Nelson v. Bowler*, the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. The argument has been fully considered, but is not persuasive. In *Nelson,* the court held that the compound of which utility was in question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in *Nelson,* the instant application does not have a showing of practical utility because the specification does not allow the skilled artisan to use the instant invention for the reasons previously discussed. It is maintained that the instant application has not established a correlation between underexpression of the PRO1357 mRNA and polypolypeptide or the diagnostic use of the encoded protein.

On pages 41-45, Appellants also cite *Cross v. Iizuka* (Fed. Cir. 1985), arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully considered, but is not persuasive. At issue is **not** whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to allow the skilled artisan to use the claimed invention without further significant research. Because as previously discussed there is critical information lacking which includes: whether differences in expression of PRO1357 nucleic acid were significant, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumors, whether mRNA levels correlated with encoded protein levels, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention.

On pages 41 and 42-43, Appellants cite *Fujikawa v. Wattanasin*, arguing that *in vitro* testing of a pharmaceutical was sufficient to support use *in vivo.* The argument has been fully

considered, but is not persuasive. At issue is not whether *in vitro* microarray/expression data can *per se* support use of differential expression for diagnostic purposes. The issue in this application is the insufficiency of disclosure to support a specific and substantial or well established utility or to allow the skilled artisan to use the claimed invention without undue experimentation. Because as previously discussed there is critical information lacking which includes: repeatability of the differential expression of PRO1357 polynucleotide both in terms of frequency/prevalence and quantity/sensitivity, under what conditions differences could be detected, and what levels (relative or absolute) were detected in tumor and normal control, the skilled artisan cannot use (whether *in vivo* or *in vitro*) the claimed invention.

Turning to the rejection under 35 USC, 112, first paragraph enablement, Appellants argue (p. 47) that based in part on "the disclosure in Example 18 of the instant application that the nucleic acid encoding the PRO1357 polypeptide is at least two-fold differentially expressed in lung and stomach tumor relative to normal lung and stomach, respectively." The argument has been fully considered, but is not persuasive. There is nothing in Example 18 to indicate that the PRO1357 nucleic acid is two-fold differentially expressed. That opinion comes from the first declaration of Dr. Grimaldi filed 9/24/04. Further, even assuming it is two-fold differentially expressed, it is maintained for the reasons for record and as discussed above, that one of skill in the art would not reasonably expect that to be true of the PRO1357 protein because of the unpredictability of mRNA/protein level correlation studies in the art.

"Appellants submit [p.49] that because the claimed polypeptides have substantial, specific and credible utility, it is not proper to reject the claimed polypeptides as lacking enablement on a "lack of utility" basis." The argument has been fully considered, but is not persuasive. First, it is maintained that the invention does not have utility. Second, MPEP § 2107.01 states that "It is important to recognize that 35 U.S.C. 112, first paragraph, addresses matters other than those related to the question of whether or not an invention lacks utility. These matters include ... whether the applicant has provided an enabling disclosure of the claimed subject matter..." Third, while part of the reasoning for lack of enablement may be applicable to lack of utility, there are additional reasons as discussed in the previous Office action mailed 6/14/05 on pages 4-5:

> Evaluation of the invention in light of factors to be considered for enablement as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is helpful in showing why the instant invention cannot be used. As to the nature of the invention, it is a polypeptide encoded by a nucleic acid with no known specific association other than that asserted by Appellants of underexpression in stomach and lung tumors. The polypeptide itself was not evaluated in the specification for actual expression in tissues. Since the encoding mRNA is expressed in stomach and lung tissue, one would reasonably expect the encoded protein also to be expressed, though at what levels it would be expressed is unknown. The protein does not have a recognized/characterized physiological/biochemical property. Proteins not identical to SEQ ID NO:78 have not been shown to exist in nature. let alone in stomach or lung tissue. As to the state of the prior art, other encoding nucleic acids usable for tumor markers had been identified, though none as a tumor marker were identical or highly similar to SEQ ID NO:77. Therefore, the connection of SEQ ID NO:77 to tumors was not known. The prior art is silent with respect to activity of PRO1357 or its relationship to a family of proteins with conserved structure and function. While the skill in the art for differential screening of nucleic acids has existed for over a decade, interpretation of the results depends, for example, on relative or absolute levels of the difference(s), the ability to generalize to more than one cell culture or tumor type or, conversely, the ability to pinpoint a particular tumor type (*e.g.*, adenocarcinoma *versus* squamal), and repeatability of the differential expression both in terms of frequency/prevalence and quantity/sensitivity. Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given. The breadth of the claims is broad, encompassing structural variation. There is very little guidance or direction about using the claimed polypeptide except that the encoded nucleic acid of SEQ ID NO:77 is underexpressed in stomach and lung tumors. As discussed in previous Office actions, the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example. For all these reasons and those previous stated, it would require undue experimentation to use the invention as claimed.

The above paragraph discusses factors to be considered for evaluating enablement of an invention, including nature of the invention, state of the prior art, level of predictability in the art, existence of working examples, breadth of claims and amount of direction or guidance by the inventors. It remains the Examiner's position that evaluation of enablement of the instant invention using the above considerations results in the conclusion that it would require undue experimentation to use the invention as claimed.

Appellants argue (p. 50-51, middle of p. 55 and second full paragraph of p. 63) that *Brana* is applicable to the present case because the enablement rejection is based on lack of

utility and that the two types of rejection are the same in the instant case. The argument has been fully considered, but is not persuasive. It is not agreed that the enablement rejection is based **totally** on lack of utility, but in the present case the enablement rejection necessary relies to a large extent on the grounds for holding a lack of utility. However, just as with the related PRO1357 polynucleotide case, there are aspects of enablement separable from that of utility, since the polynucleotide remains not enabled. The two rejections in the instant case are separable and do not stand or fall together. The applicability of *Brana* was discussed in previous Office actions and is discussed above.

Appellants argue (p. 52) that the specification enables the claimed invention for making and using it. The argument has been fully considered, but is not persuasive. Appellants are directed to the paragraph two above this. It is maintained for the reasons of record that the specification is not enabling for how to use the instant invention.

Appellants argue (p. 53) there has been no reasons set forth way claims encompassing highly related polypeptides constitute a "board" claim, and the scope of the claims weighs in favour of enablement. The argument has been fully considered, but is not persuasive. As stated in the previous *Wands* analysis, the protein does not have a recognized/characterized physiological/biochemical property and the breadth of the claims is broad, encompassing structural variation. By definition, a claim to any polypeptide not identical SEQ ID NO:78, with or without its associated signal peptide, is more broad than the narrowest claim. The scope of the claims does not weigh in favor of enablement because the claimed proteins not identical to SEQ ID NO:78 are only limited by the requirement that they may be used to make an antibody which recognizes SEQ ID NO:78 in lung or stomach tissue. This is not as broad a scope as one could easily imagine, but it is a breadth for which the instant applications fails to provide enablement since the polypeptide of SEQ ID NO:78 is not enabled. If the protein to which an antibody binds is not enabled, then an antibody which binds it and depends for enablement on that of the protein is likewise not enabled.

Appellants argue (top of p. 54) that the nature of the invention is a polypeptide which may be used as a diagnostic, so the nature of the invention weighs in favor of enablement. The argument has been fully considered, but is not persuasive. The nature of the invention has to do not only with the fact that the invention is a polypeptide, but what characteristics are attributed to

it. The sequence of the polypeptide is known, but its function is not. It is not known, for example, if it plays a role in causing cancer or if it binds a particular binding partner. That is what was meant by the Examiner's statement that the claimed invention is a polypeptide without a "recognized/characterized physiological/biochemical property". It is maintained that the use of the polypeptide for a diagnostic purpose is not enabled.

Appellants argue (p. 54 and top of p. 60 and bottom of p. 61-63) that because methods of making and using polypeptides and making and using antibodies were known in the prior art, this factor weighs in favour of enablement. The argument has been fully considered, but is not persuasive. A generic use of a polypeptide, such as a weight marker on a gel, that is applicable to almost any polypeptide does not provide enablement for the claimed polypeptide. Likewise, making an antibody that recognizes a polypeptide which is not enabled does not support enablement for the antibody.

Appellants argue (pages 55-56) that differential nucleic acid screening is not relevant to determination of enablement and as argued above in reference to expected correlation of mRNA level to protein level and applicability with *In re Brana,* one skilled in the art could use the claimed invention. The argument has been fully considered, but is not persuasive. The point the Examiner was trying to make about differential screening is that interpretation of results is based on many factors as illustrated by the work of Haynes et al., Chen et al. and Fessler et al. Also, Appellants are directed to the Examiner's discussion of mRNA/protein level correlation and *Brana* above.

Appellants argue (paragraph bridging pages 56-57) that due to the level of skill in the art, the skilled artisan would have been able to predictably use the claimed polypeptide in diagnostic methods. The argument has been fully considered, but is not persuasive. It is maintained for the reasons of record that there is unpredictability relating to correlation or lack there of between levels of an mRNA and its encoded protein based on the proteomic art of record. As stated in the above Wands analysis and present in the final Office action of 6/22/05, "Further, there is evidence in the prior art that even for those nucleic acids differentially expressed in tumors, a correlated expression for the encoded protein is not a given."

Appellants argue (pages 57-59) that the specification provides sufficient guidance and direction in the specification for the skilled artisan to be able to use the claimed invention. The

argument has been fully considered, but is not persuasive. For the reasons previously discussed, including the lack of predictability and limited teachings in the specification including relative or absolute nucleic acid expression levels and repeatability of the differential expression of PRO1357 polynucleotide both in terms of frequency/prevalence and quantity/sensitivity, it is maintained that the skilled artisan could not use the claimed invention without undue experimentation.

Appellants argue (p. 59) that the presence of working examples weighs in favor of enablement. The argument has been fully considered, but is not persuasive. The working examples fail to support enablement and do not address the specific type of tumor tissue used, levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened, for example.

Appellants argue (middle of p. 61) that the fact that further experimentation is necessary or complex does not make the experimentation undue. The argument has been fully considered, but is not persuasive. Whether experimentation is undue is one factor in determining enablement. For the polypeptide or binding antibody to be enabled, one skilled in the art must be able to use it based on the description in the specification, prior art and information generally available to one of skill in the art at the time the application was filed. Applicants are directed to the *Wands* analysis discussed above which provides reasoning why it would require undue experimentation to use the claimed invention.

Appellants argue (p. 62 and bottom of p. 63) that the Wands factors support enablement of the claimed invention and the Examiner has provided no significant evidence or argument to the contrary. The argument has been fully considered, but is not persuasive. It is maintained for the reasons previously set forth and as discussed above, the instant invention is not enabled. Appellants are referred to the discussions above that reference evidence and arguments that support the lack of enablement.

In addressing the rejection of claims under 35 USC 102, Appellants argue (pages 71-73) that the invention is entitled to a priority date no later than August 24, 2000. The argument has been fully considered, but is not persuasive. Because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, as discussed above, and the earlier application likewise do not

meet those requirements, the instant application does not receive benefit of priority to earlier filed applications. Even though SEQ ID NO:77 and 78 and the expression information of Table 18 were previously disclosed, enablement thereof has not been established as discussed above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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